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EXAMINER

LANDAU, SHARMILA GOLLAMUDI

ART UNIT

PAPER NUMBER

1611

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Continuation of Disposition of Claims: Claims pending in the application are 1-4,6,8,10-16,19-21,23,24,26,29-40,43-53,56-73,76-97,100-112,114-125 and 128-138.

Continuation of Disposition of Claims: Claims rejected are 1-4,6,8,12-16,19,21,23,24,26,29-33,36-40,43,44,112,114,118-125,131-133 and 135-138.

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DETAILED ACTION

Receipt of Request for Continued Examination, Amendments/Remarks, and the Rule 132

Affidavits filed 11/8/07 is acknowledged. Claims 1-4, 6, 8, 10-16, 19-21, 23-24, 26, 29-40, 43-53, 56-73, 76-97, 100-112, 114-125, 128-138 are pending in this application. Claims **1-4, 6, 8, 12-16, 19, 21, 23-24, 26, 29-33, 36-40, 43-44, 112, 114, 118-125, 131-133, 135-138** are directed to the elected species. Claims 10-11, 22, 25, 34-35, 45-53, 56-73, 76-97, 100-111, 115-117, 129-130, 134 are withdrawn as being directed to the nonelected species. Claims 5, 7, 9, 17-18, 27-28, 41-42, 54-55, 74-75, 98-99, 113, 126-127 stand cancelled.

Election/Restrictions

Species elected: 1) glycerol; 2) aerosol, foam, mousse, spray as the product form; and 3) alcohol as the penetrating agent.

Terminal Disclaimer

The terminal disclaimer filed on 10/30/06 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of 10/949116 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4, 6, 8, 12, 13, 15-16, 19-21, 23-24, 26, 29, 112, 114, 118-120, 121-125, 128, 131-132, 135-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 88/01863 to Peck et al in view of WO 97/12602 to Weiner et al or Yu et al (EP0273202) respectively.

Peck teaches a quick breaking foam to treat baldness comprising either (a) 1-5% minoxidil; (b) 10-50% propylene glycol; (c) 30-75% alcohol; (d) 0.5-10% emulsifier and/or surfactant; (e) 0.1-5% hydroxypropyl methylcellulose; and (f) 10-50% water wherein the composition is actuated with a propellant. See page 2. Peck teaches the minoxidil may be selected from any known analog. Peck teaches skin penetrants including alcohol such as dodecanol and oleyl alcohol. See page 5. Peck teaches various surfactants in the composition including Tween 80 (polysorbate) and Span 60 to improve the stability of the composition. See page 6, lines 20-25. Peck teaches the use of minoxidil or a salt thereof. See page 5, lines 25-30.

Peck does not teach the instant acid salt.

WO teaches a topical composition for minoxidil and teaches minoxidil is not soluble in water, acetone, and ethyl acetate and although the alcohol based solutions of minoxidil have only some penetration. See page 2. WO teaches modifying the solubility of the active in an aqueous solution by making it more hydrophilic without changing the active agent's therapeutic properties. The active agent that is more hydrophilic, has improved penetration through the hair follicle. WO teaches modifying by reacting it with a hydroxy organic acid such as lactic acid. See page 3 and 4.

Yu et al teach additives such as hydroxy acids enhance the therapeutic effects of pharmaceutical and cosmetic actives in topical treatments. See page 2. The pharmaceutical or cosmetic active is utilized generally in the amount of 0.01-40% and the hydroxyl acid is used in the amount of 0.01-99%. See page 6. Yu teaches the use of 3% lactic acid with minoxidil to help the minoxidil dissolve in the solution and enhance penetration and the efficacy of minoxidil on hair growth. The pH of the solution is 4.7. See example 3.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Peck and WO and utilize the instant minoxidil acid salt. One would have been motivated to do so since WO teaches this addition to yield a hydrophilic

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compound, allows for better penetration into the hair follicles. Alternatively, it would have been obvious to one of ordinary skill in the art at the time the invention was made combine the teaching of Peck and Yu et al and utilize the instant acid. One would be motivated to do so Yu teaches adding lactic acid dissolves minoxidil providing better penetration of minoxidil. Therefore, a skilled artisan would have been motivated to add an acid to form a minoxidil acid salt for enhanced penetration of minoxidil into the hair follicle.

Regarding the recitation of “at least 5%”, Peck teaches minoxidil in an amount of 1-5%. “At least 5%” includes 5.00001%, 5.001%, etc, which is considered obvious over the prior art’s “5%”. It would have been obvious to a skilled artisan at the time the invention was made to manipulate the concentration of minoxidil during routine optimization.

Regarding the recitation “approximately 7.5 to 12%”, the examiner directs applicant's attention to MPEP 2111.01. Applicant has not defined the term "approximately" to mean exactly. Thus, "approximately 7.5%" is given latitude.

Regarding the instantly claimed ratio of ethanol to water, Peck sets forth a general range of components wherein the alcohol is utilized in an amount of 30-75% and water from 10-50%, thus it is within the skill of an artisan to look at the guidance provided by Peck and manipulate the concentrations (ratio) of water and ethanol depending on the concentration of the other components. It should be noted that generally difference in concentrations do not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such as concentration is critical. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Regarding “consisting essentially of”, note MPEP 2111.03: The transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, “consisting essentially of” will be construed as equivalent to “comprising.”

Response to Arguments and Rule 132 Declaration

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Applicant's arguments filed 11/8/07 have been fully considered but they are not persuasive.

Applicant argues the examiner has not established a prima facie case of obviousness. Applicant argues that the PTO must satisfy three requirements. The PTO must provide a reason to combine the elements in the prior art, a reasonable expectation of success, and the reference or combination of references should teach all the claimed limitations. Applicant argues there is no motivation to modify Peck et al to incorporate an acid salt since Weiner teaches away from a minoxidil acid salt.

As acknowledged by applicant, the critical question in establishing a prima facie obviousness case is to “identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does...” KSR International Co. V. Teleflex Inc., 550 U.S. -, 82 USPQ2d 1385 (2007). In instant case and as set forth in the rejection, WO teaches this addition to yield a hydrophilic compound, allows for better penetration into the hair follicles. Yu teaches adding lactic acid dissolves minoxidil providing better penetration of minoxidil. Therefore, clearly the examiner has identified the motivation that would have prompted a skilled artisan to combine an acid to Peck's composition. Thus, a skilled artisan would have been motivated to add an acid to form a minoxidil acid salt for enhanced penetration of minoxidil into the hair follicle.

The second question is whether there is a reasonable expectation of success. In instant case and as set forth in the rejection, Peck teaches the use of minoxidil or a salt thereof. See page 5, lines 25-30. It is known in the pharmaceutical art that the addition of the acid forms a salt and thereby makes the active compound, i.e. minoxidil, more soluble. Hence, the penetration of the compound into the skin is increased. Therefore, a skilled artisan would have *reasonably* expected success in adding acid to Peck's composition.

It is incumbent upon the applicant to answer the question “whether the improvement is more than the predictable use of prior art elements according to their established functions”, which applicant has not done. It is noted that applicant argues that the addition of a salt increases minoxidil's solubility; thus requiring less co-solvent. However, as discussed above, this is a well known concept in the pharmaceutical art (the addition of the acid forms a salt and thereby makes the active compound hydrophilic and more soluble). Hence, solubilizing the active allows

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increased penetration of the compound into the skin. This is established by both WO and Yu et al. Both WO and Yu teach adding the acid makes it more soluble and increases penetration of minoxidil. Summarily, applicant has not shown any unexpected results in rebutting that it is prima facie obvious to combine prior art element to yield a *predictable result*. Further, it should be noted that, “The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965).” Applicant has not provided any factual evidence establishing unobviousness (the opinion Declaration is noted and will be discussed below).

Applicant argues that increased solubility is not equivalent to increased skin permeation.

The examiner agrees that this phenomenon does not apply to all drugs. However, in instant case, it clearly applies to minoxidil. This is established by WO and Yu et al as discussed in the preceding paragraph.

Lastly, the combination of references teaches all the claimed limitations. The instant claims are directed to a method for the treatment of hair loss and method of preparing a composition consisting essentially of A) at **least 5% of a minoxidil** or a pharmaceutically acceptable salt thereof; B) an acid; C) a solvent system comprising **water and a lower alcohol** in a ratio of 9:1 to 1:9 and a co-solvent selected from the aromatic and polyhydric alcohols; and when **the co-solvent is polyhydric alcohol, it is in an amount of less than approximately 10%.**

In instant case, Peck teaches the composition generally comprises (a) 1-5% minoxidil; (b) 10-50% propylene glycol; (c) **30-75% alcohol**; (d) 0.5-10% emulsifier and/or surfactant; (e) 0.1-5% hydroxypropylmethylcellulose; and (f) **10-50% water** wherein the composition is actuated with a propellant.

As set forth in the rejection, it is the examiner's position that the recitation of “at least 5%” is rendered obvious by Peck. “At least 5%” includes values such as 5.00001%, 5.001%, etc., which is obvious over the prior art's “5%” since it is conventional to optimize the prior art's range during routine experimentation. Similarly, it is the examiner's position that less than 10% is rendered obvious by Peck. “Less than 10%” includes values 9.9999%, 9.99%, etc., which is obvious over the prior art's 10%.

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Applicant argues that Peck does not exemplify the instant invention and only teaches a broad disclosure. Thus, applicant argues that Peck teaches away from the instant invention.

Although the examples are noted, the examiner points out that the instant rejection is made under obviousness and not anticipation. Therefore, the criteria for establishing a case of prima facie obviousness is not whether the prior art exemplifies all the claimed limitations but whether the prior art suggests the claimed limitations. As acknowledged by applicant, Peck teaches a general range. This is sufficient in establishing obviousness. Additionally, the examiner directs applicant's attention to MPEP 2123, II: "Disclosed examples and preferred embodiments **do not constitute a teaching away form the broader disclosure** or nonpreferred embodiment".

Regarding the instantly claimed ratio of ethanol to water, Peck sets forth a general range of components wherein the alcohol is utilized in an amount of 30-75% and water from 10-50%. Thus, it is within the skill of an artisan to look at the guidance provided by Peck and manipulate the concentrations (ratio) of water and ethanol depending on the concentration of the other components.

Regarding "consisting essentially of" in all the independent rejected claims, the examiner directs applicant's attention to MPEP 2111.03: The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." Page 5, of the instant specification teaches various active compounds and excipients that may be added to the composition. Thus, the specification does not provide a clear indication of what material is considered to affect the basic and novel characteristics of the composition.

Applicant argues that the instant claim language excludes lipid vesicles.

However, it is noted that the dependent claims are directed to "penetration enhancers" as excipients. The examiner points out that WO teaches that the making the drug hydrophilic and encapsulating it in the lipid vesicle increases its penetration through the skin. See page 2, line 35 to page 3, line 5. Clearly, the lipid vesicles act as penetration enhancers and thus are not excluded by the instant claim language. Regarding claim 143, the examiner points out that Peck

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teaches the instantly claimed penetration enhancers (dodecanol and oleyl alcohol). However, the instant claim language does not exclude carriers such as lipid vesicles and applicant has not pointed out how the lipid vesicles change the novel and basic characteristics for the composition.

Applicant argues that Table 1 in WO 97/12602 teaches away from the lactic acid salt addition.

The examiner notes that WO 97/12602 teaches Formula III has "twice the penetration" than any other formula as disclosed by Weiner on page 7, lines 9-11. Commercial Rogaine has the "next best" penetration. Formula III comprises a vesicle material, lactic acid, ethanol, and minoxidil. The Rogaine formulation comprised minoxidil, ethanol, water, and propylene glycol. Thus, as acknowledged by applicant, Formula III wherein the minoxidil is made hydrophilic by the addition of an acid and encapsulated has better skin penetration. As discussed above, the instant claims do not exclude the lipid vesicle. Therefore, WO does provide the motivation to combine the references. Moreover, WO clearly establishes that a polyhydric alcohol is not required to increase penetration since Formula III does not have a polyhydric alcohol. Therefore, it is reasonable to expect that the minimum range taught by Peck could be utilized since the lipid vesicle and acid addition salt to help increase penetration of minoxidil.

Moreover, the examiner points out that WO's comparison of Formula XI and commercial Rogaine is not a proper comparison that can be applied to the instant invention for the following reasons: The commercial Rogaine formulation comprises minoxidil, ethanol, water, and propylene glycol. Formula XI comprises lactic acid, minoxidil, and ethanol. However, this formulation does not comprise a glycol, which is a known penetration enhancer. Thus, obviously Rogaine would function better since it has two penetration enhancing agents (acid and a glycol) compared to Formula XI, which has one (acid). Therefore, one cannot conclude that adding an acid alone does not and cannot increase the penetration of minoxidil since both formulations in WO are not controlled with only one variable. Meaning, the same formulations containing the same excipients/carriers should have been compared, wherein minoxidil was the only variable, i.e. the minoxidil versus its acid addition salt. Other variables in the Rogaine formulation, i.e. propylene glycol, affected the penetration of minoxidil. Therefore, this argument does not show the unobviousness of the invention.

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Applicant argues that Yu only teaches a 2% minoxidil formulation and a large polyhydric content. Further, applicant argues that the use of an acid addition salt is negated by Weiner (WO 97/12602).

First, the argument that WO negates the use of an acid addition salt has been addressed in above. As discussed above, WO does not negate the use of an acid addition salt since it is not a proper comparison to commercial Rogaine. Second, the examiner notes that applicant argues against the references individually. However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is the examiner's position that Peck renders instant recitation "at least 5% minoxidil" and "less than 10%" obvious and thus Yu et al is not relied upon to cure this deficiency. Yu et al is merely relied upon to provide motivation to utilize an acid to form a salt, which is also suggested by Peck.

The Rule 132 Declaration under 37 CFR 1.132 filed 11/8/07 is insufficient to overcome the rejection of the claims as set forth in the last Office action because:

It is noted that the Declaration provided by Barry Hunt is an opinion Declaration. "Although an affidavit or declaration which states only conclusions may have some probative value, such an affidavit or declaration may have little weight when considered in light of all the evidence of record in the application." In instant case, the Declaration provided Barry Hunt only provides conclusions without any probative value, i.e. evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, etc. It appears the statements are only remarks to the Office Action in a Declaration form. Further, it is noted that Mr. Hunt makes statements such as "may be unacceptable to the consumer, and may cause local irritation" without providing evidence to substantiate such statements. Therefore, the Rule 132 Declaration is unpersuasive.

Therefore, it is the examiner's position that the instant claims are rendered obvious over Peck et al in view of WO 97/12602 or Yu et al.

Claims 14, 30-33, 36-40, 43-44, 133 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 88/01863 to Peck et al in view of WO 97/12602 or Yu et al (EP0273202) respectively in further view of Uchikawa et al (5,156,836).

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The teachings of Peck, Yu, and WO '602 have been set forth above.

Peck does not teach the elected glycerol co-solvent or the use of an antioxidant.

Uchikawa teaches a hair revitalizing composition that may comprise minoxidil.

Uchikawa teaches conventional excipients used to formulate hair-revitalizing compositions include polyhydric alcohols such as glycerine and propylene glycol, antioxidants, etc. see column 4, lines 5-30.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the above references and substitute the exemplified propylene glycol with the instantly claimed glycerol and arrive at the instant invention. One would have been motivated to do so since Uchikawa teaches both propylene glycol and glycerol are polyhydric alcohols conventionally used in the art. Therefore, a skilled artisan would have expected similar results absent unexpected results by using any conventional polyhydric alcohol known in the art in the composition. Further, it would have been obvious for a skilled artisan to further utilize a conventional excipient such as an antioxidant as taught by Uchikawa to prevent oxidation.

Response to Arguments

Applicant's arguments filed 11/8/07 have been fully considered but they are not persuasive.

Applicant argues the merits of Peck et al, WO, and Yu et al, which has been addressed above and incorporated herein.

Applicant argues that Uchikawa does not teach or suggest an acid salt. However, this argument is unpersuasive since it is the examiner's position that WO and Yu et al cure this deficiency and Uchikawa is only relied upon to teach the instant co-solvent.

Therefore, it is the examiner's position that the instant claims are rendered obvious over Peck et al in view of WO 97/12602 or Yu et al in further view of Uchikawa.

Claims 1-4, 6, 8, 12-13, 15-16, 19, 20-21, 23-24, 26, 29, 30-31, 36-37, 39-40, 43-44, 112-113, 118-125, 128, 131-132, 135-136, 138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Di Schiena (4866067) in view of Yu et al (EP0273202).

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Di Schiena discloses minoxidil (0.1-10%, ex: 5%) combined with oxyniacic acid for topical treatment of alopecia. The reference discloses that minoxidil is insoluble in water and the salt form of minoxidil is soluble in a water-based composition. Therefore, an acid makes it remarkably soluble in water without loading the composition with glycols. Di Schiena discloses a foam composition containing the instant active, water, a lower alcohol, cetyl alcohol (penetration agent), propellant, laureth-4, and propylene glycol (9%) in a foam composition (note examples). The foam composition also contains cetyl alcohol and a surfactant (stabilizer). Di Schiena teaches methanol, ethanol, or isopropanol as suitable solvents (col. 2, lines 17-20 and examples). Further, the reference exemplifies a lotion containing the active without the use of a glycol, instant amount of water, ethanol, and active (example b). The examples teach a variety of water to lower alcohol ratios. Di Schiena teaches the use of antioxidants in the compositions.

Di Schiena does not teach the use of lactic or acetic acid.

Yu et al teach additives such as hydroxy acids enhance the therapeutic effects of pharmaceutical and cosmetic actives in topical treatments. See page 2. The pharmaceutical or cosmetic active is utilized generally in the amount of 0.01-40% and the hydroxyl acid is used in the amount of 0.01-99%. See page 6. Yu teaches the use of 3% lactic acid with minoxidil to help the minoxidil dissolve in the solution and enhance penetration and the efficacy of minoxidil on hair growth. The pH of the solution is 4.7. See example 3.

It is would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Di Schiena and Yu et al and add a hydroxyl acid such as lactic acid to the composition. One would have been motivated to do so since Yu teaches adding lactic acid dissolves minoxidil providing better penetration of minoxidil. Therefore, a skilled artisan would have been motivated to add an acid to form a minoxidil acid salt for enhanced penetration of minoxidil into the hair follicle. The use of a conventional excipient in the aerosol formulation is obvious since Di Schiena teaches the use of an antioxidant in the other formulations.

Regarding the instantly claimed ratio of ethanol to water, it would have been obvious to one of ordinary skill in the art at the time the invention was made to look to manipulate the parameters set forth in Di Schiena. One would have been motivated to do so as part of routine experimentation to yield the best possible results. Differences in concentration do not extend

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patentability to subject matter encompassed in the prior art unless there is evidence-indicating criticality.

Regarding “consisting essentially of”, note MPEP 2111.03: The transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, “consisting essentially of” will be construed as equivalent to “comprising.” It is noted that Di Schiena teaches reacting oxyniacic acid and minoxidil to form the compound of formula I, i.e. a minoxidil salt, which reads on a pharmaceutically acceptable salt of minoxidil and thus the instant claim language does not exclude the prior art’s acid.

Response to Amendment

Applicant argues that the claims have been amended in accordance to the Rule 132 Declaration.

The Declaration under 37 CFR 1.132 filed 5/30/06 is insufficient to overcome the rejection of claims based upon Di Schiena in view of WO 97/12602 because:

Although the examiner notes applicant has amended the claims to recite the ratio, the examiner notes the following. DiSchiena utilizes 5% minoxidil derivative in example (e) and the instant claims recite "at least 5%" minoxidil or a derivative thereof. However, the Rule 132 Declaration utilizes 4.75% minoxidil. Further, the excipients in each composition are different and the minoxidil amount is different. The examiner points out that in showing the criticality of the instant water to alcohol ratio, the ratio must be the only variable. However, the inventive composition is not controlled since it contains different excipients and the minoxidil amount is different. Therefore, the examiner cannot conclusively determine if the unexpected property, i.e. the inventive composition is homogenous, is caused by the amount of minoxidil, the addition of lactic acid, and citric acid, etc, or the solvent/water ratio.

Therefore, the Rule 132 Declaration is considered to be unpersuasive.

Claims 1-4, 6, 8, 12-13, 15-16, 19-21, 23-24, 26, 112, 118-125, 128, 131-132, 135-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 07-048230 in view of

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WO 97/12602 or Yu et al (EP0273202) respectively in further view of Caldini et al (4,272,516).

JP '230 teaches a hair tonic with hair restoring properties comprising 0.1-10g minoxidil, 30-70g ethanol and water. See abstract.

JP does not specifically teach adding an acid or a cosolvent.

WO teaches a topical composition for minoxidil and teaches minoxidil is not soluble in water, acetone, ethyl acetate and although the alcohol based solutions of minoxidil have only some penetration. See page 2. WO teaches modifying the solubility of the active in an aqueous solution by making it more hydrophilic without changing the active agent's therapeutic properties. The active agent that is more hydrophilic, has improved penetration through the hair follicle. WO teaches modifying by the pH reacting it with a hydroxy organic acid such as lactic acid. See page 3 and 4.

Yu et al teach additives such as hydroxy acids enhance the therapeutic effects of pharmaceutical and cosmetic actives in topical treatments. See page 2. The pharmaceutical or cosmetic active is utilized generally in the amount of 0.01-40% and the hydroxyl acid is used in the amount of 0.01-99%. See page 6. Yu teaches the use of 3% lactic acid with minoxidil to help the minoxidil dissolve in the solution and enhance penetration and the efficacy of minoxidil on hair growth. The pH of the solution is 4.7. See example 3.

Caldini et al teach a process for improving transcutaneous and transfollicular absorption of cosmetic compositions in the amount of 5-33.33%. See abstract. Caldini teaches benzyl alcohol has the ability of facilitating the absorption of the other components through the skin and its associated organs. See column 1, lines 10-20. The cosmetic compositions include a lotion for reactivating the hair, a reactivating jelly, a tonic milk, and a reactivating cream. See column 4, lines 40-45. **Caldini teaches a reactivating lotion for the hair that comprises comprising a solvent system of 4% propylene glycol, 12% benzyl alcohol, 31.5% water, and 47.5% ethanol. See example 1.** Both PPG and benzyl alcohol read on the co-solvent. Further, benzyl alcohol reads on the penetration agent.

It is would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of JP and WO and utilize the instant minoxidil acid salt. One would have been motivated to do so since WO teaches this addition to yield a hydrophilic

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compound, allows for better penetration into the hair follicles. Alternatively, it would have been obvious to one of ordinary skill in the art at the time the invention was made combine the teaching of JP and Yu et al and utilize the instant acid. One would be motivated to do so Yu teaches adding lactic acid dissolves minoxidil providing better penetration of minoxidil. Therefore, a skilled artisan would have been motivated to add an acid for enhanced penetration of minoxidil into the hair follicle.

It would have been obvious at the time the invention was made to combine the teachings of the above references and utilize benzyl alcohol in the solvent system. One would have been motivated to do so since Caldini et al teach the use benzyl alcohol in an amount of 5-33.33% improves transcutaneous and transfollicular absorption of active agents, especially hair reactivating composition. Thus one would expect an additive effect of increasing penetration of the composition by adding benzyl alcohol in JP's composition.

Regarding the instantly claimed ratio of ethanol to water, JP teaches 30-70g ethanol and water and this sets forth a general range of components. Thus, it is within the skill of an artisan to look at the guidance provided by JP and manipulate the concentrations (ratio) of water and ethanol depending on the concentration of the other components. It should be noted that generally difference in concentrations do not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such as concentration is critical.

Regarding "consisting essentially of", note MPEP 2111.03: The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising."

Response to Arguments

Applicant's arguments filed 11/8/07 have been fully considered but they are not persuasive.

Applicant argues against the merits of Weiner et al (WO 97/12602) and Yu et al, which have been addressed above and incorporated herein.

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Applicant argues that Caldini does not cure the deficiencies of addition of an acid.

Caldini is only relied upon to teach the co-solvent and applicant has not addressed this. Thus, it is the examiner's position that the JP in view of Weiner et al or Yu et al in further view of Caldini et al renders the claims as amended obvious.

Claims 1-4, 6, 8, 12-13, 15-16, 19-21, 23-24, 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/03638 to Navarro et al in view of WO 97/12602 to Weiner et al.

Navarro teaches the solvent system comprising the combination of ethanol or isopropyl alcohol and propylene glycol or polyethylene glycol solubilize minoxidil but the significant amount of propylene glycol makes the hair greasy and shiny. See page 2 of translation. Navarro teaches using cyclodextrin to reduce the amount of solvent required to solubilize minoxidil. See page 3 of the translation. Navarro teaches a hair care composition containing 0.1-7% minoxidil, 0.1-5% cyclodextrin, 0.5-15% minoxidil solvent (propylene glycol), 30-50% monoalcohol (ethanol or isopropanol), and water. Note abstract and examples.

Navarro does not teach the use of lactic or acetic acid.

Weiner teaches a topical composition for minoxidil. WO discloses that making materials more hydrophilic, improves penetration through the hair follicle. Weiner teaches that a number of different modifications may be made to the minoxidil. One such modification is provided by reacting minoxidil with an organic acid such as lactic acid. The minoxidil may also be converted to a salt by reacting it with a cyclodextrin. See page 3. Weiner states that the use of a minoxidil acid salt addition provides substantial penetration and cyclodextrin salt addition is the "next best". See page 7. Weiner teaches encapsulation of minoxidil increase penetration of the active across the skin.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Navarro et al and Weiner et al and substitute Navarro's cyclodextrin with the instant acid to convert minoxidil into a salt. One would be motivated to do so since Weiner teaches that by converting minoxidil to a hydrophilic compound, it penetrates the skin penetrate. More specifically, Weiner teaches the conversion of minoxidil into a salt form by reacting it with an organic acid such as instant lactic acid or with cyclodextrin and notes that

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although both provide penetration of minoxidil, the acid salt addition has a better effect than the cyclodextrin salt addition. Therefore, one would have been motivated to use an acid salt addition to convert minoxidil into a hydrophilic compound rather than Navarro's cyclodextrin since Weiner teaches the acid salt addition has better penetration into the skin. With regard to the pH recited in the dependent claims, it is the examiner's position that the combination of Navarro and Weiner would yield a pH since the lactic acid would render a pH in the acidic range. The examiner cites Yu et al (EP '202) to support this position wherein lactic acid and minoxidil yield a composition with a range of 4.6.

With regard to the instantly claimed ratio, Navarro sets forth a general range of components wherein a monoalcohol is utilized in an amount of 30-50% and water to balance, thus it is within the skill of an artisan to look at the guidance provided by Navarro and manipulate the concentrations (ratio) of water and ethanol depending on the concentration of the other components. It should be noted that generally difference in concentrations do not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such as concentration is critical. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Regarding "consisting essentially of", note MPEP 2111.03: The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising."

With regard to claim 4, the lower limit of *approximately* 7.5% is considered obvious over Navarro's teaching that the minoxidil may be in the amount of 7%. A skilled artisan would have been motivated to manipulate the concentration of active, i.e. increase the amount of minoxidil, in the composition depending on the desired "strength" of the composition.

Note that the hair tonic reads on the elected species "spray" since the composition is capable of being sprayed.

Response to Arguments and Rule 132 Declaration

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Applicant's arguments filed 11/8/07 have been fully considered but they are not persuasive.

Applicant argues the merits of Weiner et al.

The merits of Weiner et al have been addressed above and incorporated herein. The examiner reiterates that Weiner's Table 1 does not conclusively teach away from the acid addition since a proper comparison has not been made. Briefly, WO's compares Formula XI and commercial Rogaine. The commercial Rogaine formulation comprises minoxidil, ethanol, water, and propylene glycol. Formula XI comprises lactic acid, minoxidil, and ethanol. However, this formulation does not comprise a glycol, which is a known penetration enhancer. Thus, obviously Rogaine would function better since it has two penetration enhancing agents (acid and a glycol) compared to Formula XI, which has one (acid). Therefore, one cannot conclude that adding an acid alone does not increase the penetration of minoxidil since both formulations in WO are not controlled with only one variable. Meaning, the same formulations containing the same excipients/carriers should have been compared, wherein minoxidil was the only variable, i.e. the minoxidil versus its acid addition salt. Other variables in the Rogaine formulation, i.e. propylene glycol, affected the penetration of minoxidil.

Applicant argues that the instant claim language excludes Weiner's lipid vehicle and cyclodextrin.

The examiner points out that Weiner teaches modifying minoxidil with either an acid or cyclodextrin. Thus, the premise of the rejection is that it would have been obvious to substitute the prior art's cyclodextrin with an acid since the prior art teaches both compounds are used to solubilize minoxidil, i.e. both are functional equivalents. Therefore, there is a reasonable expectation of success. Moreover, Weiner teaches modifying minoxidil with acid provides better penetration than modifying it with cyclodextrin. Note the comparison of Formula XI to IX and X.

Applicant argues that cyclodextrin and minoxidil have a host-guest configuration that imparts the solubility properties. Applicant argues that cyclodextrin is unstable in an acid environment. Applicant provides a Rule 132 Declaration to substantiate this argument.

The Rule 132 Declaration filed 11/8/07 is insufficient to overcome the rejection of the claims based upon WO 97/03638 to Navarro et al in view of WO 97/12602 to Weiner et al as set forth in the last Office action because:

The examiner acknowledges Mr. Abram's Declaration that cyclodextrin and minoxidil have a host-guest configuration, which imparts the solubility properties. The examiner notes that that cyclodextrin is unstable in an acid environment, which would “destroy” its ability to solubilize the drug. However, the premise of the rejection is to substitute cyclodextrin with instant acids. The premise is not to add an acid to Navarro's composition. Further, the examiner points out that the fact that cyclodextrin and acids have different mechanisms of imparting solubility to a drug, both still act to solubilize a drug. Therefore, applicant's arguments and the Rule 132 Declaration are unpersuasive.

Regarding the instant claim language, the examiner again points out that the premise of the rejection is the substitution of one solubilizing agent with another irrespective of the lipid vesicle. It should be noted that the examiner is not attempting to incorporate Weiner's entire disclosure into Navarro's disclosure. The examiner points out that, “the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.” See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). As discussed above, Weiner makes a comparison of minoxidil with cyclodextrin and lactic acid, respectively, *without* a lipid vesicle. Weiner demonstrates that minoxidil modified with an acid provides better penetration than modifying it with cyclodextrin. Thus, clearly the lipid vesicle is not required. Although, it is noted that Weiner's invention is directed to the lipid vesicle plus the acid, which provides a superior penetrating effect, Weiner nonetheless teaches making a compound more hydrophilic by adding acids increases penetration. Note MPEP 2123: “The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain.”

Thus, it is the examiner's position that the Navarro et al in view of Weiner et al renders the instant claims *prima facie* obvious.

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Claims 14, 30-33, 36-40, 43-44, 112, 118-125, 128, 131-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/03638 to Navarro et al in view of WO 97/12602 to Weiner et al in further view of Wong et al (5,130,142).

The teachings of Navarro and Weiner have been set forth above.

The references do not teach the elected glycerol cosolvent or a propellant.

Wong teaches a hair growth formulation. Wong teaches a composition in solution form can be applied to the skin as is, or else can be formulated into an aerosol and applied to the skin as a spray-on. To formulate an aerosol composition, a suitable propellant is used to expel the contents of the container. See column 9, lines 10-15 and column 12, lines 16-25. Further, Wong teaches solvents include glycerol, propylene alcohol, polyethylene glycol, butanediol are solvents. Other conventional excipients include antioxidants and emulsifiers. Wong teaches the use of skin emollients including cetyl alcohol.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the above references and further utilize a propellant. One would have been motivated to do so if one desired administering the solution as a spray-on since Wong teaches a propellant allows a solution to aerosolize (expel from the container). Further, it would have been obvious to use either propylene glycol or glycerol and arrive at the instant invention. One would have been motivated to do so since Wong teaches both are solvents conventionally used in the art. Further, a skilled artisan would have expected similar results absent unexpected results since both are polyhydric alcohol. Additionally, the use of a conventional excipient such as an antioxidant, emulsifiers, and emollients. One would have been motivated to add an antioxidant if one desired to prevent oxidation. Lastly, it would have been obvious to utilize cetyl alcohol (reads on penetration enhancer and higher alcohol) for its emollient properties as taught by Wong.

Response to Arguments

Applicant's arguments filed 11/8/07 have been fully considered but they are not persuasive.

Applicant argues that Wong does not cure the deficiency of Navarro and Weiner. The merits of Navarro and Weiner have been discussed above and incorporated herein. Wong is only

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relied upon to teach the co-solvent and a propellant, which applicant has not addressed. Thus, it is the examiner's position that the Navarro in view of Weiner et al in further view of Wong et al renders the claims as amended obvious.

Claims 30-31, 36-40, 43-44, 112, 114, 118-125, 128, 131-132, 135-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/03638 to Navarro et al in view of WO 97/12602 to Weiner et al in further view of WO 88/01863 to Peck et al.

The teachings of Navarro and Weiner have been set forth above.

The references do not teach the instant excipients claimed in independent claim 61 (propellant, a higher alcohol, antioxidant, and stabilizer) or independent claim 143 (specific skin penetration enhancers).

Peck teaches a quick breaking foam to treat alopecia (loss of hair on the scalp) comprising either (a) 1-5% minoxidil; (b) 10-50% propylene glycol; (c) 30-75% alcohol; (d) 0.5-10% emulsifier and/or surfactant; (e) 0.1-5% hydroxypropylmethylcellulose; and (f) 10-50% water wherein the composition is actuated with a propellant. See page 2. Peck teaches the minoxidil may be selected from any known analog. Peck teaches skin penetrating enhancers including alcohol such as dodecanol and oleyl alcohol. See page 5. Peck teaches various surfactants in the composition including Tween 80 (polysorbate) and Span 60 to improve the stability of the composition. See page 6, lines 20-25. Peck teaches the use of minoxidil or a salt thereof. See page 5, lines 25-30. The method of making the composition is taught in the examples.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the above references and further utilize the instant excipients. One would have been motivated to utilize a propellant, if one desired administering the solution as a spray-on since Peck teaches a propellant allows a solution to aerosolize (expel from the container). Second, it would have been obvious to utilize instant higher alcohols since Peck teaches the use of dodecanol and oleyl alcohol to increase skin penetration of minoxidil. Thus, a skilled artisan would have been motivated to further add a higher alcohol to provide an additive affect of enhancing the penetration of minoxidil thorough the skin. Third, it would have been obvious to utilize a surfactant such as those taught in Peck since Peck teaches various surfactants stabilize compositions. Thus, one would have been motivated to add a surfactant to increase stability of the composition.

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Claims 1-4, 6, 8, 12-13, 15-16, 19-21, 23-24, 26, 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bazzano (5183817) in view of WO 97/12602 or Yu et al (EP0273202) respectively.

Bazzano teaches a minoxidil composition to increase growth rate and stimulate new hair growth by administering a lotion containing 0.01-0.1% retinoic acid or its ester (note this reads on penetration enhancer), 0.5-5% minoxidil, ethanol, 5-50% propylene glycol, 0.1% BHT, and distilled water (up to 10%). Formulation example II contains 1% retinoic acid, 10% minoxidil, 4% cetyl alcohol, 4% ethanol, and up to 100% water. Bazzano teaches the use of pharmaceutically acceptable acid salt. See column 19, lines 1-25. Bazzano states that minoxidil or its derivatives and analogs that are described in US patents 5910928, 3637697, 3461461, 4139619, and 4596812 are incorporated into the reference. US patent 3,461,461 teaches the acid salt derivatives including lactic acid and other instantly claimed acids of minoxidil. Bazzano discloses that a major problem in influencing hair growth is obtaining good percutaneous absorption of the active compounds. The retinoid compounds cause excellent absorption of the hair follicles. See column 19, lines 35-40. The formulation can contain any pharmaceutically acceptable carrier, additive, or solubilizer.

Although Bazzano states that a minoxidil derivative/analog may be utilized, Bazzano does not explicitly teach the use of an acid addition.

WO teaches a topical composition for minoxidil and teaches minoxidil is not soluble in water, acetone, ethyl acetate and although the alcohol based solutions of minoxidil have only some penetration. See page 2. WO teaches modifying the solubility of the active in an aqueous solution by making it more hydrophilic without changing the active agent's therapeutic properties. The active agent that is more hydrophilic, has improved penetration through the hair follicle. WO teaches modifying by reacting it with an hydroxy organic acid such as lactic acid. See page 3 and 4.

Yu et al teach additives such as hydroxy acids enhance the therapeutic effects of pharmaceutical and cosmetic actives in topical treatments. See page 2. The pharmaceutical or cosmetic active is utilized generally in the amount of 0.01-40% and the hydroxyl acid is used in the amount of 0.01-99%. See page 6. Yu teaches the use of 3% lactic acid with minoxidil to help

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the minoxidil dissolve in the solution and enhance penetration and the efficacy of minoxidil on hair growth. The pH of the solution is 4.7. See example 3.

It is would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Bazzano and WO and utilize the instant minoxidil acid salt. One would have been motivated to do so since WO teaches this addition to yield a hydrophilic compound, allows for better penetration into the hair follicles. Further, since Bazzano is concerned with penetration of the composition into the hair follicle one would expect an additive effect of increasing penetration of the composition by adding instant salt. A skilled artisan would have reasonably expected success and similar results since Bazzano also teaches the acid salts may be utilized and incorporated other US patents wherein the instant acid salt is taught.

Alternatively, it would have been obvious to one of ordinary skill in the art at the time the invention was made combine the teaching of Bazzano and Yu et al and utilize the instant acid. One would be motivated to do so Yu teaches adding lactic acid dissolves minoxidil providing better penetration of minoxidil. Therefore, a skilled artisan would have been motivated to add an acid for enhanced penetration of minoxidil into the hair follicle. Moreover, one would have expected similar results by the instant combination since Bazzano suggests the use of an acid addition salt.

Regarding the instantly claimed ratio, Bazzano sets forth a general range of components wherein water is utilized in an amount up to 10% and ethanol is to balance, thus it is within the skill of an artisan to look at the guidance provided by Bazzano and manipulate the concentrations (ratio) of water and ethanol depending on the concentration of the other components. It should be noted that generally difference in concentrations do not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such as concentration is critical. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Regarding “consisting essentially of”, note MPEP 2111.03: The transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a

clear indication in the specification or claims of what the basic and novel characteristics actually are, “consisting essentially of” will be construed as equivalent to “comprising.”

Response to Arguments

Applicant's arguments filed 11/8/07 have been fully considered but they are not persuasive.

Applicant argues that the instant claims language excludes retinoic acid since it affects the basic and novel characteristics of the composition. Applicant argues that Bazzano teaches retinoic acid is an essential ingredient in the formulation. Thus, applicant argues that a skilled artisan would not have been motivated to exclude Bazzano's retinoic acid.

Applicant's arguments filed 11/30/06 have been fully considered but they are not persuasive. Applicant's attention is directed to MPEP 2111.03. The transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, “consisting essentially of” will be construed as equivalent to “comprising.” Page 5, of the instant specification teaches various active compounds and excipients that may be added to the composition. Thus, the specification does not provide a clear indication of what material is considered to affect the basic and novel characteristics of the composition. Further, certain claims allow for penetration enhancers. The examiner notes that Bazzano teaches retinoid compounds “cause excellent percutaneous absorption”. See column 19, lines 35-40. Further, US 2003212077, paragraph 00014 also discloses retinoic acid it is a known penetration enhancer. Therefore, it is clear that penetration enhancers are not excluded by the instant claim language.

Conclusion

All the claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila Gollamudi Landau whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30).

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Sharmila Gollamudi Landau/
Primary Examiner, Art Unit 1611